Patent
Attorney Docket: 892,280-210
(Formerly 342312004300)

REMARKS

Applicants thank the Examiner for taking time on November 5, 2004, to discuss the pending Office Action. Applicants explained that the present invention runs counter to conventional wisdom that, for several groups of widely used antibiotics, including penicillins, cephalosporins, carbapenems, and glycopeptide antibiotics (a class to which dalbavancin belongs), time over MIC is the important parameter that controls outcome. As explained during the call, Applicants' invention is based on the unexpected result that, for dalbavancin, outcome can be greatly improved using infrequent dosing, where each dose is separated by five to ten days.

Reconsideration of the rejections set forth in the Office Action mailed September 9, 2004, is respectfully requested. Claim 1-56 have been canceled. Claim 57 has been amended. Claims 62-78 have been newly added. New claim 62 is a dependent claim directed to treatment of skin and soft tissue infection. Please be advised that the FDA now refers to "skin and soft tissue infection (SSTI)" as "skin and skin structure infection (SSSI)." Claims 57-78 remain pending in this case. Specification support for these amendments and new claims can be found at, e.g., page 5, lines 17-27; page 6, lines 3-6; page 16, line 4 – page 17, line 6; page 19, line 13 – page 22, line 11; and page 29, line 1 to page 39, line 17. Therefore, these amendments are made without introducing new matter.

Amendments to the Specification

As requested by the examiner, applicants have amended the specification to include the serial numbers of the co-pending applications that were filed concurrently.

Art Rejections

Claims 1-61 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as being allegedly unpatentable over Hackbarth, et al. (ASM, May 2001, Abstract No. A-4), Hackbarth et al. (May 2001, Poster No. A-4), Jabes et al. (41st ICAAC Abstracts, Chicago, IL, September 22-25, 2001, Abstract No. B-989, p. 54), Jabes et al. (41st ICAAC Abstracts, Chicago, IL, September 22-25, 2001, Abstract No. B-1654, p. 68), or Leighton, et al. (41st ICAAC Abstracts, Chicago, IL, September 22-25, 2001, Abstract No. 951, p. 25).

Claims 1-56 have been canceled. Therefore, the rejections of these claims are now moot. Claims 57-61 and new claims 62-78 are directed to treatment of bacterial infection using a dosing regimen that includes at least initial and subsequent therapeutically effective doses of dalbavancin, wherein each dose is separated by about five to ten days or, in the case of claims 59, 61, 75, and 77, approximately one week.

As explained in our discussion on November 5, 2004, the conventional wisdom for several groups of widely used antibiotics, including penicillins, cephalosporins, carbapenems, and glycopeptide antibiotics (a class to which dalbavancin belongs), is that the time during which the serum concentrations exceed the minimum inhibitory concentration (MIC) of the pathogen (T > MIC) is the best predictor of efficacy. This general principle is well known for β-lactams,[1]

[1] See, e.g., BURGESS, D.S. et al. *"Pharmacokinetics and Pharmacodynamics of Piperacillin/Tazobactam When Administered by Continuous Infusion and Intermittent Dosing."* CLIN THER. 2002 Jul;24(7):1090-1104 ("Although intermittent bolus dosing is currently the standard of practice for many antimicrobial agents, beta-lactams exhibit time-dependent bacterial killing. Maximizing the time above the minimum inhibitory concentration (MIC) for a pathogen

vancomycin,[2] and teicoplanin.[3] Therefore, the prior art teaches that smaller, frequent doses are preferred over larger, infrequent doses in order to maintain serum concentrations above the MIC, while at the same time avoiding toxicity. In fact, under this principle, optimization is achieved by keeping serum concentration just above MIC by frequent administration, e.g., intravenous administration. By maintaining the lowest possible level that is just above MIC, toxicity is believed to be minimized.

Contrary to this conventional wisdom, applicants have unexpectedly discovered a dramatic increase in efficacy by administering doses of dalbavancin at intervals of about 5-10 days, or alternatively, at approximately a week. Tables 4 and 5, located on pages 33 and 34 of the specification, respectively, show the results of such a regimen. As seen in Table 4, the

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is the best pharmacodynamic predictor of efficacy. Use of a continuous infusion has been advocated for maximizing the time above the MIC compared with intermittent bolus dosing." (Abstract) (Attached as Exhibit A)

[2] MacGowan, A.P. "Pharmacodynamics, Pharmacokinetics, and Therapeutic Drug Monitoring of Glycopeptides" THEREAPEUTIC DRUG MONITORING 20: 473-477 (1998) ("The pharmacodynamics of glycopeptides studied in several animal models support the concept that high initial concentrations offer no advantage in bacterial killing or mortality, whereas higher, sustained concentrations or more frequent dosing have improved survival in animal models of infective endocarditis.") (P. 473) (Attached as Exhibit B)

ROSS, Gigi H. et al. "Glycopeptide Pharmacodynamics" in ANTIMICROBIAL PHARMACODYNAMICS IN THEORY AND CLINICAL PRACTICE. 177-204 (2002) ("On the basis of limited in vitro studies, T > MIC appears to most closely predict efficacy of vancomycin. Therefore, the length of time the antibiotic concentration exceeds the MIC of the offending organism and not the height of the peak above the MIC, as in aminoglycosides, should be considered the goal of the dosing of vancomycin.") (P. 184) (Attached as Exhibit C)

[3] HARDING, I. et al., "*Teicoplanin Therapy for Staphylococcus aureus septicaemia: relationship between pre-dose serum concentrations and outcome.*" J. ANTIMICROBIAL CHEMOTHERAPY 45: 835-841 (2000) ("These data would indicate that transient high peak serum concentrations of teicoplanin are not likely to be of benefit in killing bacteria or curing infection and that sustained concentrations over the MIC will be of benefit in terms of improving extravascular drug penetration and cure rates.") (P. 839) (Attached as Exhibit D)

clinical success rate ("clinically evaluable at FU") shows a dramatic increase in efficacy for the two-dose regimen (94.1 %) compared to the single dose regimen (61.5 %), even though both maintain serum concentration above MIC for the intended course of treatment. Similarly, in Table 5, the two-dose regimen had a success rate of 87.5 % against the total organisms tested, as compared to a rate of 43.8 % for the single dose regimen, even though both maintain serum concentration above MIC for the intended course of treatment. This dramatic improvement in efficacy was completely unexpected and contrary to the teaching of the prior art, which suggested a daily dosing regimen for dalbavancin. (See, e.g., Jabes et al, Abstract B-989 "Data from studies in animal models and from Phase 1 clinical studies support a once daily dosing regimen for DA.") The prior art for dalbavancin and for other glycopeptide antibiotics therefore teaches away from the claimed invention.

Claims 57 and 73 are therefore patentably distinct from the cited art. (*See In Re Soni*, 54 F.3d 746, 751, 34 U.S.P.Q.2d 1684, 1688 (Fed. Cir. 1995) "when an applicant demonstrates substantially improved results, ... and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary.") Claims 58-72 and 74-78 are dependent on claims 57 and 73, respectively, and are therefore patentably distinct from the cited art for the same reasons applicable to claims 57 and 73. The rejections based on prior art should therefore be withdrawn.

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Information Disclosure Statement

Applicants note that the PTO-Form 1449 submitted September 9, 2004 was not returned to Applicants with initials in the left-most column. Applicants respectfully request that the Examiner return a copy of PTO-Form 1449 with the next correspondence.

CONCLUSION

For all the foregoing reasons, applicants assert that the claims are in condition for allowance. Favorable action on the merits of the claims is therefore earnestly solicited. If any issues remain, please contact the applicants' undersigned representative at (949) 737-2900. The Commissioner is hereby authorized to charge any fees that may be required in connection with the filing of these documents to Deposit Account No. 50-2862.

Respectfully submitted,

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By: John Kappos
John Kappos
Reg. No. 37,861

JCK/DKW/cp

O'Melveny & Myers LLP
114 Pacifica, Suite 100
Irvine, CA 92618
(949) 737-2900

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